Rezulin

Press Accounts

Is FDA Too Quick to Clear Drugs?
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When Jo Ann Ottmers began taking her new diabetes medicine, the drug suddenly made it much easier for the 59-year-old diabetic to keep her blood sugar levels from rising dangerously high. But soon the Kansas City, Mo., woman began feeling nauseated and weak.

Ottmers finally stopped taking the drug after discovering on the Internet that the medicine could cause rare but life-threatening liver damage. But her health continued to decline, and 16 months after she began taking the drug she was forced to undergo a liver transplant. She has since sued Warner-Lambert, the company that makes the drug, Rezulin.

Warner-Lambert insists that Rezulin is safe if patients are monitored closely. Nevertheless, because of dozens of cases like Ottmers's – 28 deaths and seven liver transplants linked to the drug – the FDA this week will consider whether regulation of its use should be tightened.

The questions about Rezulin, however, illustrate a larger debate that is raging over the safety of the medicines that millions of Americans take every day. Pressured by Congress, AIDS activists and drug companies in recent years, the historically sluggish FDA had to remake itself. Today, the agency is approving more drugs every year than ever before, taking half the time to do it.

Consumer advocates, and even some of the agency's own drug reviewers, argue that the agency has become too cozy with the pharmaceutical industry and too lax, putting lives at risk. Five drugs have been pulled off the market over the last two years – a record for such a short time – after dozens of deaths were linked to their use.

The FDA insists that its vetting processes are still the world's gold standard for safety. "I do not believe the standards have been lowered," said Murray Lumpkin, who heads the agency's drug safety programs. "There is no way that we will completely eliminate the risk from the process – if we have drugs with no risks, we will have no drugs."

The record number of drugs pulled off the market is, in fact, in line with the historic 2 percent to 3 percent withdrawal rate for new drugs, said Kenneth I. Kaitin, director of the Tufts University Center for the Study of Drug Development. With so many new medicines being approved, Kaitin said, the number of withdrawals is bound to climb as well. "We're still not any different and not any greater than we have been in the past," he said.

But even if the rate of problem drugs has not increased, drug safety experts say the increased pace of drug approvals means that more problems are bound to make it onto the market. To guard against that, drug safety experts argue that more should be done to conduct follow-up studies on the safety of these drugs after they arrive on pharmacy shelves to catch problems early.

"My concern isn't these disasters – my concern is the disasters that are underway that we don't know about," said Brian Strom, a professor of medicine at the University of Pennsylvania. "No one's minding the store."

Critics point out that the FDA's lead reviewer of Rezulin, John Gueriguian, opposed its approval and was removed from considering the application. Gueriguian said he found the company's safety testing inadequate and its claims of efficacy unconvincing. Even more, he said, his review of animal studies and clinical trials that revealed rare signs of jaundice signaled that the drug had hidden dangers. Nevertheless, the FDA approved the drug in March 1997 with exceptional speed because it offered a new way to control diabetes.

The FDA said it does not remove reviewers because of their positions on drugs but would not elaborate on why Gueriguian was removed. Warner-Lambert officials say Gueriguian used inappropriate language in criticizing the company and its application during meetings in September 1996. An affidavit by a Warner-Lambert official supplied to The Washington Post by the company referred to a Sept. 25, 1996, meeting in which "Dr. Gueriguian removed a bottle of what appeared to be cologne from his desk and said that he had to pour it over the [application] because it smelled 'like garbage'," and excrement. "Later during the meeting, he said that it had been about a half-hour and that 'the [application] was starting to smell again' and pretended to pour the cologne over the boxes containing the [application].'."

As large numbers of patients began taking Rezulin, the liver damage reports started to come into the agency's system for monitoring drug side effects. As evidence mounted that some patients could be harmed or even killed by the drug, the agency changed the labeling on the drug – not once but three times – to require more extensive testing of patient liver function. Since that time, confirmed reports of damage linked to Rezulin have dropped, but unconfirmed reports of liver damage continue to come into the agency. A Washington-based consumer advocacy organization, Public Citizen's Health Research Group, has filed a petition demanding that the agency remove Rezulin from the market.

Patients who believe they have benefited from Rezulin say they would hate to see the drug pulled. "I would half-kill to stay on it," said Laura Wilson-Perry of Memphis. "But if something came along that would regulate my blood sugar in the same way, I'd jump to it in a second because I don't want to risk liver problems."

Drug safety experts say the tests designed to ferret out problems ahead of time can only detect so much. The tests required for new drugs typically involve from 1,500 to 6,000 patients – too few to catch a drug reaction that might be experienced by less than 1 in 10,000 patients. The trials also are too brief to catch reactions that might emerge over years of use. That means the current system of testing drugs is fated to miss uncommon reactions until it reaches a broader market, making the drug-taking public guinea pigs in an ongoing experiment.

Americans could demand that more patients be tested before a drug can be approved – say, 100,000 patients to find reactions that might affect 1 in 20,000, Lumpkin said. And regulators could demand to see the effects of a drug taken over years. Obviously, however, "there is a cost to that – a cost not only in dollars but a cost in time" during which patients cannot take medicines that might help them.

The fact that problems might not be detected on the front end of drug approval means the agency must do everything it can to catch side effects after approval, safety advocates say. But while the agency is working to upgrade what it calls "postmarket surveillance," it still depends largely on a system of reporting by doctors and companies that probably only catches about 1 percent of such adverse events, according to Raymond Woosley of Georgetown University Medical School. Agency officials point out that this is still enough to send up a red flag for many safety problems, although it does not allow a precise accounting.

The FDA is buried under the 150,000 reports that flow in each year, agency insiders say. And 1992 legislation that brought in industry funds to speed up review times prohibits the use of that money for

postmarket surveillance – a fight the agency lost against the industry, said former FDA commissioner David A. Kessler. "That's where we fell down," Kessler said. "We didn't go to the wall."

In a recent article in the Journal of the American Medical Association, Timothy Brewer of Harvard University called for the FDA to go beyond its current reporting system, which relies on doctors and companies to report suspected problems. Brewer advocates more extensive use of data collected by medical researchers and others to sift for drug reactions.

Woosley goes further. He proposes creating a drug safety agency independent of the FDA so the regulators who approve drugs are not responsible for figuring out what they did wrong when disaster strikes. "When a plane crashes, you don't ask the FAA if their standards are wrong," Woosley said.

Another problem, however, is that the FDA cannot control how doctors prescribe the medications it regulates. Today's health care system gives doctors and patients less time to discuss medication and its risks, and patients increasingly demand medicines that they have heard about through drug company advertising. So even though the agency had explicitly warned doctors not to prescribe Duract for more than 10 days at a time, physicians prescribed it for longer periods; four patients died and eight required liver transplants before the drug was withdrawn. Similarly, the FDA warned doctors that Posicor could kill patients if taken with some 25 other drugs, yet hundreds of patients had life-threatening reactions.

"If we're getting to a point where we're getting a standard of drug approval that says we can only approve drugs after we have second-guessed how they will be misused and how to keep the misuse from happening, that's going to be a very difficult standard," said the FDA's Lumpkin.

Drug safety advocates urge the creation of new programs to better educate doctors on the one hand and more systematically look for side effects on the other. "We still need to get drugs approved more quickly," Woosley said. "It's not a problem with the drugs, it's a problem with the way they're used and a safety system that doesn't catch problems quickly enough."

Even Gueriguian, who has retired from the FDA and now works as a consultant to drug companies, believes the agency is merely adjusting to a new system of approvals and has not gone seriously astray. "If anyone says the whole system has gone to pot, they are vastly exaggerating," he said.

Charles Flexner of the Johns Hopkins University Medical School said the FDA was right to speed up its processes, but "we are making a societal trade-off here." More people will be injured from unanticipated side effects, Flexner said, but at the same time far more people can benefit from the presence of new drugs on the market. "This is a very tough line that the FDA has to walk," he said.

For doctors and patients, the wisest course might be to let others take the early risk. Gail Povar, a primary care internist in Silver Spring, said she rarely prescribes a new drug in its first year on the market.

When patients demand a new drug, she makes sure they understand that they are taking part in "an experiment. . . . I have never felt that it was appropriate to jump on a bandwagon, whole hog, when a new drug comes out," she said, "unless it's a syndrome for which there are no other options. You simply don't know what the rare lethal or sublethal clinical side effect is going to be."